Remarks

Claims 1-11 and 61-62 are pending in this application. New claims 61-62 are added to recite free thalidomide and thalidomide salt or solvate, respectively. Support for these claims can be found, for example, on page 14, lines 15-17 of the specification. No new matter has been introduced.

Applicants appreciate the Examiner's withdrawal of the rejections under 35 U.S.C. § 112. Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 103 should also be withdrawn for at least the following reasons.

On pages 2-4 of the Office Action, the rejection of claims 1-11 as allegedly obvious over Marx *et al.*, *Proc. Am. Soc. Clin. Oncology* 18: 454a (1999) ("Marx"), in view of Pitot *et al.*, *Journal of Clinical Oncology* 15(8): 2910-2919 (1997) ("Pitot") and U.S. Patent No. 5,622,959 to Priel *et al.* ("the '959 patent") is maintained. In particular, it is contended that because Marx allegedly discloses an antiangiogenic effect of thalidomide and Pitot and the '959 patent allegedly disclose antitumor activities of CPT-11 and CPT, respectively, the claimed invention is obvious. Applicants respectfully traverse this rejection.

The claimed invention is not obvious over Marx in combination with Pitot and the '959 patent at least because: 1) no *prima facie* case of obviousness is established in this case because the references do not provide the required motivation or suggestion to combine; and 2) even if a *prima facie* case of obviousness was established, sufficient unexpected results were shown in the disclosure to rebut any presumption of obviousness. *See* Response of August 17, 2003, pages 6-7.

In response to Applicants' argument that there would have been little motivation in view of the fact that thalidomide, at the time of this invention, was not an approved anticancer agent, the Examiner contends that such a fact is irrelevant because Marx teaches the anti-tumor activity of thalidomide. Office Action, pages 2-3. Applicants respectfully traverse the contention of the Examiner; as well-settled, the Examiner must consider the art as a whole, *i.e.*, Marx cannot be considered in a vacuum. *See, e.g.*, *Manual of Patent Examining Procedure*, § 2141 (citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966)).

In this regard, Applicants respectfully point out that there were numerous known anti-tumor agents at the time of this invention other than thalidomide, some of which had been approved for the treatment of cancer. Furthermore, none of the references cited by the Examiner provide any suggestion

that thalidomide would have any usefulness when used in combination with a topoisomerase inhibitor, much less particularly usefulness. Consequently, Applicants respectfully submit that, when the art is considered as a whole, those of ordinary skill in the art would not have been motivated to use thalidomide in combination with a topoisomerase inhibitor.

Furthermore, and perhaps more important, is the fact that this application properly provides an unexpected synergy between thalidomide and a topoisomerase inhibitor (*e.g.*, irinotecan). Despite this fact, the Examiner dismisses Applicants' submission that any presumption of obviousness is rebutted, alleging that "the feature upon which applicant relies (i.e., co-administration of thalidomide and irinotecan to patients with colorectal cancer) are not recited in the rejected claims." Office Action, page 3. Applicants respectfully disagree.

Applicants respectfully point out that the pending claims properly recite all of the features that the Examiner refers to. For example, claim 1 clearly recites the co-administration of thalidomide and a topoisomerase inhibitor (of which irinotecan is a member) to a patient with cancer (of which colorectal cancer is a member).[1]

Applicants note that the Examiner may be contending that the scope of the pending claims should be limited to "irinotecan" and "colorectal cancer," instead of "a topoisomerase inhibitor" and "cancer."[2] However, Applicants point out that the test results provided in the specification is only illustration, and Applicants are entitled to the full scope of the claims. This is because it was known at the time of this invention that various topoisomerase inhibitors can be used for the treatment of cancer. *See, e.g.*, Abstracts of Sugiura *et al.*, *Gan To Kagaku Ryoho*, 19(13): 2140-5 (1992), Chau *et al.*, *Free Radic Biol Med.*, 24(4): 660-70 (1998), and Paz-Ares *et al.*, *Brit. J. Cancer*, 78(10): 1329-36 (1998), all of which are attached hereto as Exhibit A (disclosing anticancer activity of topoisomerase inhibitors CPT-11, topotecan, IST-622, β-lapachone, and GI-147211).

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[1] Applicants respectfully point out that claims 4 and 7 recite colon or rectal cancer and irinotecan, respectively, and these claims may be separately patentable from claims 1 and 2.

[2] Applicants respectfully point out that, to the extent the Examiner appears to contend that the scope of the claims is too broad, such rejection is inappropriate under 35 U.S.C. § 103.

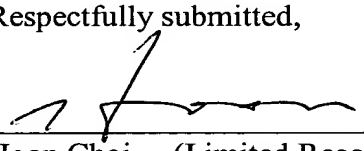
In addition, it was known that irinotecan (and thus other various topoisomerase inhibitors) can be used for the treatment of various types of cancer. *See*, Hecht, *Oncology*, 12(8 Suppl. 6): 72-8 (1998) ("Hecht"), attached hereto as Exhibit B. Hecht teaches that irinotecan "demonstrates activity against a broad spectrum of malignancies, including carcinomas of the colon, stomach, and lung." Furthermore, Hecht also teaches that irinotecan is generally associated with gastrointestinal toxicities, *i.e.*, the adverse effects are not limited to where it is used for the treatment of colorectal cancer. Therefore, Applicants respectfully submit that they are entitled to the full scope of the claims as pending. Consequently, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

Conclusion

For at least the foregoing reasons, Applicants respectfully submit that claims 1-11 are allowable. No fee is believed due for this submission. However, should any fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date June 24, 2005



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1: Gan To Kagaku Ryoho. 1992 Nov;19(13):2140-5.

[DNA topoisomerase inhibitor]

[Article in Japanese]

Sugiura T, Ariyoshi Y.

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CPT-11 and Topotecan are a new semisynthetic derivative of CPT, and have been shown to inhibit DNA topoisomerase I and to have a strong antitumor activity with low toxicity against murine tumor. On the other hard, the new antitumor compounds, NC-190 and IST-622 have been shown to inhibit DNA topoisomerase II, and the clinical study are currently under progress. A phase II study of CPT-11 demonstrated that CPT-11 was a very active agent which a acceptable toxicities against patient with advanced non-small cell lung cancer and small cell lung cancer.

Publication Types:
- Review
- Review, Tutorial

PMID: 1332623 [PubMed - indexed for MEDLINE]

1: Free Radic Biol Med. 1998 Mar 1;24(4):660-70.

ELSEVIER FULL-TEXT ARTICLE

Involvement of hydrogen peroxide in topoisomerase inhibitor beta-lapachone-induced apoptosis and differentiation in human leukemia cells.

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Beta-Lapachone a novel topoisomerase inhibitor, has been found to induce apoptosis in various human cancer cells. In this study we report that a dramatic elevation of hydrogen peroxide (H2O2) in human leukemia HL-60 cells following 1 microM beta-lapachone treatment and that this increase was effectively inhibited by treatment with antioxidant N-acetyl-L-cysteine (NAC), ascorbic acid, alpha-tocopherol. NAC strongly prevented beta-lapachone-induced apoptotic characteristics such as DNA fragmentation and apoptotic morphology. However, treatment of HL-60 cells with another topoisomerase inhibitor camptothecin (CPT) did not induce H2O2 production as compared to untreated cells. NAC also failed to block CPT-induced apoptosis. Correlated with these findings, we found that cancer cell lines K562, MCF-7, and SW620, contained high level of intracellular glutathione (GSH), were not elevated in H2O2 and were resistant to apoptosis after treatment with beta-lapachone. In contrast, cancer cell lines such as, HL-60, U937, and Molt-4 which have lower level of GSH, were readily increased of H2O2 and were sensitive to this drug. Furthermore, ectopic overexpression of Bcl-2 in HL-60 cells also attenuated beta-lapachone-induced H2O2 and conferred resistance to beta-lapachone-induced cell death. Beta-Lapachone at the concentration as low as 0.25 microM effectively induced HL-60 cells to undergo monocytic differentiation, as evidenced by CD14 antigenicity and alpha-naphthyl acetate esterase activity. Again, the beta-lapachone-induced monocytic differentiation was suppressed by NAC. These results suggest that intracellular H2O2 generation plays a crucial role in beta-lapachone-induced cell death and differentiation.

PMID: 9559879 [PubMed - indexed for MEDLINE]

1: Br J Cancer. 1998 Nov;78(10):1329-36.

A phase I clinical and pharmacokinetic study of the new topoisomerase inhibitor GI147211 given as a 72-h continuous infusion.

Paz-Ares L, Kunka R, DeMaria D, Cassidy J, Alden M, Beranek P, Kaye S, Littlefield D, Reilly D, Depee S, Wissel P, Twelves C, O'Dwyer P.

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GI147211 is a novel, totally synthetic camptothecin with promising preclinical and early clinical activity. This study was designed to determine the maximum tolerated dose of GI147211 as a 72-h infusion and to describe its pharmacokinetics and pharmacodynamics on this schedule. In a single-arm, rising-dose study in patients with advanced cancer, eight cohorts of three or more patients received 72-h infusions of GI147211 at doses ranging from 0.25 to 2.5 mg m(-2) day(-1). Forty-four patients received a total of 124 cycles. All patients had refractory tumours and 40 had received prior chemotherapy and/or radiotherapy. Whole-blood GI147211 lactone, total blood and total concentrations were measured during and over the 12 h following the infusion. Myelosuppression was observed at all dose levels. Neutropenia was dose limiting at 2.0 mg m(-2) day(-1) in minimally pretreated patients, while both neutropenia and thrombocytopenia were limiting at 1.5 mg m(-2) day(-1) in those more heavily pretreated. Phlebitis occurred with infusions through peripheral veins early in this study, necessitating the use of central venous access. Other toxicities included mild nausea and vomiting, fatigue, headache, central venous catheter infections and alopecia. Three partial and two minor responses lasting 8-34+ weeks were noted in patients with ovarian, colon and breast carcinomas and hepatoma. Mean steady-state concentrations of GI147211 increased with dose over a range of 0.25-1.24 ng ml(-1). The mean terminal elimination half-life was 7.5 h, and the clearance averaged 1074 ml min(-1) m(-2) over the doses studied. The mean fractional excretion of unchanged drug in urine was 0.114. GI147211 lactone exposure correlated with haematological toxicity. The recommended phase II doses for this regimen are 1.75 mg m(-2) day(-1) and 1.2 mg m(-2) day(-1) for minimally pretreated and heavily pretreated patients respectively. At these doses, steady-state GI147211 concentrations within the range of those effective in vitro were achieved. Extensive phase II evaluation of this compound and further phase I trials evaluating more prolonged infusions are ongoing.

Publication Types:

1: Oncology (Huntingt). 1998 Aug;12(8 Suppl 6):72-8.

Gastrointestinal toxicity or irinotecan.

Hecht JR.

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Irinotecan (CPT-11 [Camptosar]) is an important new chemotherapeutic drug that demonstrates activity against a broad spectrum of malignancies, including carcinomas of the colon, stomach, and lung. Unfortunately, frequent and often severe gastrointestinal toxicities, particularly diarrhea, have limited its more widespread use. A cholinergic syndrome resulting from the inhibition of acetylcholinesterase activity by irinotecan is frequently seen within the first 24 hours after irinotecan administration but is easily controlled with atropine. Late diarrhea occurs in the majority of patients, however, and is National Cancer Institute (NCI) grade 3 or 4 in up to 40%. The late syndrome appears to be related to the effects on the bowel of SN-38, the active metabolite of irinotecan, which undergoes biliary excretion and inactivation. Early recognition and treatment of late diarrhea with high-dose loperamide have reduced, although not entirely eliminated, patient morbidity. Further study is needed to identify the mechanism of irinotecan-induced late diarrhea and to evaluate potential new therapies.

Publication Types:
- Review
- Review, Tutorial

PMID: 9726096 [PubMed - indexed for MEDLINE]